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EXAMINER
WAGNER, R

ART UNIT	PAPER NUMBER
182	5

DATE MAILED: 04/27/89

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-21 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-21 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The drawings are objected to because the lanes in Figures 4-6 are not identified. Correction is required.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and confusing. In step (a) as presently claimed, at least some of the "plurality of pairs" can be identical, but the outcome with such an occurrence is unclear. That is, a utility problem may exist, but for the sake of brevity a utility rejection has not been made. There is no requirement that each pair be different. The "plurality of pairs" can be in a hybridized form again causing an inoperability condition to arise in subsequent steps since hybridization cannot occur with already hybridized member probes. The ratio of "amplification probe" to "amplification sequence" is unstated so self-annealing of the amplification probes can occur with method-defeating regularity. A semicolon should replace the period at the end of this step. In step (b), it is unclear whether the "amplification probes" can be incompletely hybridized to the "amplification sequence"; if not, they can hybridize with each other and then separate during step (d). At step (e), the result will be only a number of complementary copies of the amplification sequence if this sequence is a single strand originally, since there

is no provision for hybridization to a complementary sequence in the preceding steps. In claims 1, 14, 19, and 21, the meaning of "same" in "same hybridizing member" is unclear. Claim 6 is vague and confusing. In step (b), it is unclear what constitutes "an interaction"; for example, is a hydrophobic interaction envisioned? In step (c), the method to detect the hybridized detection probes is unknown, i.e. there is no positive recitation of the detection procedure. Finally, in steps (a) and (b), it is unclear if each detection probe must be complementary to portions of two ligated nucleic acid segments, or the detection probes can be shorter than the nucleic acid segments but be contiguous at the same juncture as the ligated nucleic acid segments. It is unclear how the method allows detection of three or more ligated nucleic acid segments.

Claims 7 and 8 are vague and confusing since it is unclear that the method distinguishes hybridized from nonhybridized labeled probes, i.e. an operability problem can exist. Claim 8 is further vague because the meaning of "proximity" is unclear. Claim 9 is vague because it does not give a positive recitation of the detection method for the ligated detection product, similar to the detection problem of claim 6.

Claim 14 is vague and confusing. In step (a) as

presently claimed, at least some of the "plurality of pairs" can be identical, but the outcome with such an occurrence is unclear. That is, a utility problem may exist, but for the sake of brevity a utility rejection has not been made. There is no requirement that each pair be different. The "plurality of pairs" can be in a hybridized form, again causing an inoperability condition to arise in subsequent steps since hybridization cannot occur with already hybridized member probes. The ratio of "amplification probe" to "amplification sequence" is unstated so self-annealing of the amplification probes can occur with method-defeating regularity. In step (b), it is unclear whether the "amplification probes" can be incompletely hybridized to the "amplification sequence"; if not, they can hybridized with each other and then separate during step (d). It is unclear how more than one amplification probe member can hybridize to "an amplification sequence" of step (a). In step (f) it is unclear what constitutes "an interaction"; for example, is a hydrophobic interaction envisioned ? In step (g), the method to detect the hybridized detection probes is unknown, i.e. there is no positive recitation of the detection procedure. In steps (e) and (f), it is unclear if each detection probe must be complementary to portions of two ligated nucleic acid segments, or the detection probes can be shorter than

the nucleic acid segments but be contiguous at the same juncture as the ligated nucleic acid segments. In step (e), there is not antecedent basis for "amplification probe segment." Finally, as presently stated the result at step (g) is only one "hybridized detection probe" so detection can be impossible to achieve. Claim 15 is vague for the same reason as claim 9.

Claim 19 is vague and confusing. It is unclear what constitutes an amplification sequence. The "plurality of pairs" can be in a hybridized form, thus making this reagent component to be inoperable for its intended use. Claim 20 is vague and confusing. It is unclear whether the reagent or the nucleic acid sequence has three or more ligated nucleic acid segments. It is unclear what constitutes "an interaction"; for example, is a hydrophobic interaction envisioned? It is unclear if each detection probe must be complementary to portions of two ligated nucleic acid segments, or the detection probes can be shorter than the nucleic acid segments but be contiguous at the same juncture as the ligated nucleic acid segments. It is unclear how the two detection probes can be used to detect three ligated nucleic acid segments. Claim 21 is vague and confusing. The "plurality of pairs" can be in a hybridized form, thus making this reagent component to be inoperable for its intended use. It is unclear what constitutes "an

interaction"; for example, is a hydrophobic interaction envisioned? It is unclear if each detection probe must be complementary to portions of two ligated nucleic acid segments, or the detection probes can be shorter than the nucleic acid segments but be contiguous at the same juncture as the ligated nucleic acid segments. It is unclear how the two detection probes can be used to detect three ligated nucleic acid segments.

Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to the joining of amplification probes by bonds that are not separated during subsequent steps. See MPEP 706.03(n) and 706.03(z).

The specification does not show that such bonding types as hydrogen bonding or hydrophobic bonding will remain during subsequent procedural steps.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability

> shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 19-21 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al (EPO) that uses two hybridization probes in a hybridization assay for a specific nucleic acid sequence. The two probes have nucleic acid sequences such that they can hybridize contiguous to each other when the target sequence complementary to both probes is present. Following hybridization, the contiguous probes are ligated by an enzyme or other chemical process, the ligated probes are denaturedly separated from the target strand, and after electrophoretic separation the ligated nucleic acid sequence is detected by a label that was attached to one of the probes. The unlabeled probe can have a reagent attached to it that can specifically react with an immobilized complementary reagent to allow label detection on a solid support when ligation has occurred. Kits with the appropriate reagents are also shown by Whiteley et al. It would have been obvious to provide the probes of Whiteley et al as pairs of complementary nucleic acid sequences because the probes were synthesized as the

complementary strands of the target sequence, so it would have been a routine procedure to synthesize complementary strands of the originally synthesized probes.

Claims 1-5 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al in view of Mullis et al.

Mullis et al shows an amplification procedure for detecting a specific nucleic nucleic acid sequence where two probes that specifically hybridize with sequences on opposite sides of the complementary strands that include the target nucleic acid sequence. Following hybridization of these probes, extension from the probes through the target sequence and the probe sequence on the opposite side is accomplished, the complementary strands are separated for use as templates for another cycle of probe hybridization, extension, and strand separation. At least at the final cycle, labeled nucleotides are added for incorporation into the extension product for subsequent detection purposes. It would have been obvious to perform the procedure of Whiteley et al through several cycles in order to amplify the target sequence present in a sample in view of Mullis et al. It would have been obvious to include more probes in the Whitely-Mullis procedure for the expected lower probability of unspecific probe hybridization as Whiteley et al

disclose.

Claims 6-13 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al in view of Palva et al, Palva et al shows hybridization assays for a target nucleic acid sequence where different labeled and unlabeled subsequences are ligated together. The labeled probes can be constructed so they will contiguously hybridize to the target sequence. It would have been obvious to use the technique of Whiteley et al to detect ligated nucleic acid sequences in view of Palva et al. i.e. the probes of Whitely et al to detect the ligated sequences of Palva et al in hybridization procedures. It would have been obvious to use proximity labels in the Whiteley-Palva procedure for the expected signal generated when the reactive components combine in the hybridization process.

Claims 14-18 are rejected under 35 U.S.C. 103 as being unpatentable over Whiteley et al in view of both Mullis et al and Palva et al.

It would have been obvious to sequentially perform the Whiteley-Mullis and Whiteley-Palva hybridization procedures for the expected amplification, as Mullis et al shows, and specificity, as Whiteley et al and Palva et al shows, the combination would provide.

Any inquiry concerning this communication should be directed to Richard Wagner at telephone number 703-557-3434.

RW
Wagner-fg

4/10/89

Esther M. Kepplinger

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PRIMARY EXAMINER
ART UNIT 182